REMARKS

I. Petition for Extension of Time

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office action mailed April 21, 2005 for three months from July 21, 2005 to October 21, 2005. Authorization is given to charge the extension of time fee of $1020.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

II. Claim Rejections - 35 U.S.C. § 102(b)

Claims 29 and 36-40 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by US 5,723,458 to Brieaddy et al. ("Brieaddy").

Brieaddy discloses formulations comprising an IBAT inhibitor selected from a disclosed genus of 1,4-benzothiazepines for the treatment of conditions in which inhibition of bile acid uptake is indicated. Examples of these conditions are hyperlipidemia and atherosclerosis (Abstract). The examples disclose enteric-coated compositions including the active ingredient and povidone, a wet granulation binder.

A. Brieaddy does not disclose a bile acid binder having a release coating layered directly thereon.

Claim 29 has been amended to clarify that the ingredient comprising the bile acid binder must have a release coating layered thereon for delivery of the bile acid binder to the colon. Support is provided by the specification at page 11, lines 26-27.

At page 3 of the Office Action mailed February 22, 2002, the Examiner stated that Brieaddy "does not teach the specific release locations as recited by the claims". In the present Office Action, the Examiner now alleges that the disclosure by Brieaddy of enteric-coated tablets anticipates the formulation of claim 29 and claims 36-40 which are either directly or indirectly dependent on claim 29. As previously stated, claim 29 is characterized by a bile acid binder having a delayed release membrane applied thereon. This is a structurally and functionally different arrangement from the formulation disclosed by Brieaddy wherein the entire dosage form, e.g., a tablet, rather than any one core ingredient , is enteric-coated. Therefore, it is not

possible to find each and every feature of the claimed invention in Bricaddy. Accordingly, Brieaddy fails to anticipate.

B. The Examiner incorrectly equates Brieaddy's use of povidone as an excipient to the bile acid binder as used in the claimed invention.

In connection with the obviousness rejection under 35 U.S.C. §103, the Examiner states on Page 4, Paragraph 10 of the Office Action, that "[i]t is the position of the examiner that any polymer in mixture with the IBAT inhibitor and released properly would act as a bile acid binder". Accordingly, in support of the anticipation rejection under 35 U.S.C. §102, it appears that the Examiner is equating Brieaddy's use of povidone, as disclosed in the examples, to the bile acid binder as used in the claimed invention.

Applicants respectfully disagree. There is no enabling disclosure provided by Brieaddy to use povidone, or any other polymeric excipient, for a therapeutic or medicinal effect. This is consistent with descriptions provided by suppliers of povidone. For example, povidone (or polyvinylpyrrolidone) is a polymeric material known for its use as a wet granulation binder. (See http://www.pformulate.com/povidone.htm). Although the cited website discloses that povidone may be used as a delayed release polymer, there is no disclosure or suggestion of the targeted release of povidone to the colon to bind bile acids to decrease gastrointestinal side-effects, e.g., diarrhea, particularly when caused by an increased concentration of bile acids in the colon following administration of an IBAT inhibitor. Accordingly, Applicants submit that it is incorrect to characterize the use of povidone, or any other polymeric excipient, as being pharmacologically equivalent to a bile acid binder as contemplated by the claimed invention.

C. Summary

Bricaddy does not disclose a bile acid binder having a release coating layered directly thereon for the targeted release of the bile acid binder in the colon. Brieaddy's use of povidone for the known application as a wet granulation binder does provide an enabling disclosure of its use as a bile acid binder. As such, there is no enabling disclosure of the targeted release of povidone, or any bile acid binder for that matter, to the colon to bind bile acids to decrease gastrointestinal side-effects, e.g., diarrhea.

For all of the foregoing reasons, Applicants submit that Brieaddy fails as an anticipatory reference. Specifically, Brieaddy does not disclose each and every feature of the invention of claims 29 and 36-40. Therefore, the rejection of these claims under §102(b) is improper and should be withdrawn.

III. Claim Rejections - 35 U.S.C. §103(a)

Claims 33-35 and 41-45 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Brieaddy in view of US 5,614,220 to Hirakawa et al. ("Hirakawa") and US 5,994,391 to Lee et al. ("Lee"). Applicants submit that the claimed invention cannot be derived from the cited prior art.

A. The cited prior art does not disclose or suggest the claimed invention.

The Examiner states that the primary reference to Brieaddy discloses an enteric-coated benzothiazepine tablet. The Examiner acknowledges this time, however, that Bricaddy does not disclose the target site of the IBAT inhibitor or a method for the treatment of hypercholesterolemia. Accordingly, the Examiner relies on Hirakawa in support of the allegation that the targeted release of an active is well within the level of skill of the person of ordinary skill in the art. Lee is cited for its disclosure that various IBAT inhibitors, including 1,4-benzothiazepine, are used to treat hypercholesterolemia.

In the first instance, Applicants submit that none of the references, whether taken alone or in combination, suggests combining hypercholesterolemic drugs with bile acid binders. As stated above in Section II.B., Brieaddy's use of the polymeric excipient povidone as a wet granulation binder is not an enabling disclosure of the use of a bile acid binder as a therapeutic or medicinal agent for the treatment of diarrhea during administration of an IBAT inhibitor. Furthermore, for the sake of argument, even if the prior art disclosed or suggested combining hypercholesterolemic drugs with bile acid binders, there is no suggestion that the IBAT inhibitor is layered with a delayed release membrane for delivery to the ileum whereas the bile acid binder is layered with a delayed release binder to the colon (See specification at page p.11, lines 25-27).

The secondary reference to Hirakawa discloses that it is possible to obtain a pharmaceutical preparation wherein release of *a* medicinal active ingredient is intended to occur

at the lower ileum, the ascending colon or the transverse colon (col. 4, lines 14-18). Specifically, Hirakawa suggests a pharmaceutical formulation providing the targeted release of *one* active ingredient. There is no suggestion by Hirakawa of the claimed formulation comprising *two* active ingredients wherein the active ingredients are released in different locations of the digestive tract for different therapeutic purposes. None of the medicinal active ingredients disclosed by Hirakawa include a bile acid binder which is coating layered for the targeted release in the colon (col. 4, lines 24-37). Advantageously, the claimed formulation provides for a combination therapy for treating hypercholesterolemia and diarrhea during administration of the IBAT inhibitor compound.

Lee does not remedy the deficiencies of Brieaddy and Hirakawa to suggest combining hypercholesterolemic drugs and bile acid binders having distinct release profiles as claimed.

B. The Examiner's position regarding the nature of the bile acid binder is flawed.

The Examiner states that Applicants recite that the bile acid binder is a resin (claim 42) and that this reads broadly on any polymer. Without further limitation regarding the resin, the Examiner alleges that "any polymer in mixture with an IBAT inhibitor and released properly would act as a bile acid binder".

For purposes of establishing patentability, Applicants submit that the resinous or non-resinous nature of the bile acid bile is secondary. In certain embodiments of the invention, such as those recited in pending claims 37 and 42, the bile acid binder can be a resin. In other embodiments of the invention, the bile acid binder is a non-resinous substance. The only limitation on the bile acid binder is that it be able to bind to bile acids when the bile acid binder is released in the colon.

Of primary relevance is the fact that none of the cited references, whether taken alone or in combination, suggest combining hypercholesterolemic drugs with bile acid binders. Brieaddy's use of the polymeric excipient povidone as a wet granulation binder is not an enabling disclosure of the use of a bile acid binder as a therapeutic or medicinal agent for the treatment of diarrhea during administration of an IBAT inhibitor. There is no suggestion that the

IBAT inhibitor is layered with a delayed release membrane for delivery to the ileum whereas the bile acid binder is layered with a delayed release binder to the colon.

For all of the foregoing reason, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, the rejection of claims 33-35 and 41-45 is improper and should be withdrawn.

CONCLUSION

Upon entry of this Amendment, claims 29 and 33-45 remain pending. Applicants respectfully submit that claims 29 and 33-45 are in condition for allowance. Prompt issuance of a Notice of Allowance is earnestly solicited.

The Assistant Commissioner is hereby authorized to charge any fee due in connection with this communication to Deposit Account No. 23-1703.

Dated: 14 Oct 25 2005

Respectfully submitted,

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